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PREPARATION OF DIAZOACETIC ESTERS

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This invention relates to the diazotization of glycine esters and more particularly to a new and improved process for the production of diazoacetic esters.

In the preparation of diazoacetic esters, there are employed aqueous mineral acids, such as sulfuric acid, together with a nitrate, such as sodium nitrate. However, diazoacetic esters such as ethyl diazoacetate are extremely sensitive to aqueous acids, and undergo in their presence, decomposition with liberation of nitrogen (Organic Syntheses, vol. 24, p. 57, note 2; Sidgwick's Organic Chemistry of Nitrogen, Taylor and Baker (1937), p. 352). In attempting to avoid or minimize this undesirable action, previous processes require a series of six or more successive partial diazotizations, each of which involves an incremental addition of mineral acid immediately followed by a rapid ether extraction of the partially diazotized starting materials. These previous processes thus involve tedious, complicated and time-consuming procedures. Diethyl ether used as a solvent in the diazotization process affords practically no protection against the aqueous acids. Furthermore, diethyl ether is too expensive and also extremely hazardous for use in commercial applications because of its volatility, inflammability and tendency to peroxide formation.

It is an object of this invention to provide a new and improved process for the diazotization of glycine esters to diazoacetic esters. A further object is to avoid or minimize the decomposition of diazoacetic esters in the diazotization of glycine esters in acid media. A still further object is to provide a process in which substantially complete diazotization of a glycine ester to a diazoacetic ester can be effected in essentially one step. Another object is to provide a process for producing diazoacetic esters in excellent yields from the diazotization of glycine esters. Other objects will appear hereinafter.

These objects are accomplished by the following invention which comprises diazotization of a salt of a glycine ester in the presence of a liquid aliphatic halogenated hydrocarbon solvent of one to two carbon atoms. It has now been discovered that these liquid aliphatic halogenated hydrocarbon solvents afford such a high degree of protection for the diazoacetic esters from acid environment that excellent yields of the esters can be obtained in essentially one step by diazotization of a salt of a glycine ester in their presence.

The reaction which takes place is shown by the following equation representing the diazotization of the hydrochloride of ethyl glycinate in the

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presence of methylene chloride as the aliphatic halogenated hydrocarbon solvent.

$$HCl\cdot NH_2CH_2CO_2C_2H_5 + NaNO_2 \xrightarrow[(H_2O)]{(H_2SO_4)} N_2CH{-}CO_2C_2H_5 + NaCl + 2H_2O$$

The liquid aliphatic halogenated hydrocarbons of one to two carbon atoms may be used as solvents in this invention and particularly those boiling within the range of 35° to 125° C. These latter aliphatic hydrocarbon halides are the most readily available as well as the cheapest and can be most easily separated from the diazoacetic ester. The saturated aliphatic hydrocarbon halides are especially useful as solvents in this invention, although unsaturated aliphatic hydrocarbon halides, such as tetrachloroethylene, may be employed. It is preferred to employ as a solvent a liquid aliphatic hydrocarbon halide boiling at least 20–30° C. above or below, and preferably below, the particular diazoacetic ester being prepared.

The process of this invention is generally applicable to the diazotization of any glycine ester, that is, any aminoacetic acid ester, to the corresponding diazoacetate. However this invention is particularly applicable to the hydrocarbon esters of glycine which have the general formula

$$NH_2{-}CH_2{-}\overset{O}{\overset{\|}{C}}{-}OR$$

wherein R is a hydrocarbon radical, and preferably a saturated hydrocarbon radical. More particularly preferred, because of their ease of preparation and availability, are the alkyl esters of glycine, that is, where R is an alkyl radical in the general formula.

Any salt of these glycine esters is suitable for use in this invention, such as the hydrochloride, sulfate, phosphate, acetate, propionate, and the like, although the hydrochloride is usually preferred because of greater water solubility and ease of reaction. These glycine ester salts are dissolved in sufficient water to effect complete solution at the temperature of diazotization. In general, a 10–50% aqueous solution, depending on the water solubility of the particular glycine ester diazotized, is satisfactory.

In a more detailed and preferred practice of this invention, alkyl diazoacetic esters are prepared by the process which comprises acidification of a cold aqueous solution of a mixture of the glycine ester hydrochloride and sodium nitrate with a dilute acidic reactant, such as sulfuric acid, in

the presence of an aliphatic halogenated hydrocarbon solvent, such as methylene chloride, and isolating by distillation the alkyl diazoacetic ester so formed.

The practice of this invention is further illustrated by the following examples in which parts are by weight unless otherwise indicated.

Example I

A solution of 140 parts of ethyl glycinate hydrochloride and 250 parts of water was placed in a four-necked round bottom flask fitted with a stirrer, dropping funnel, thermometer and nitrogen inlet tube. Methylene chloride (802 parts) was added and the stirred mixture cooled to −5° C. by means of a dry ice-acetone bath. Stirring was continued throughout the following reaction. A cold solution of 83 parts of sodium nitrite in 250 parts of water was added and the flask was then flushed out with nitrogen. When the temperature of the mixture had dropped to −9° C., the addition of 95 parts of 5% sulfuric acid was started. The addition of the acid required about 3 minutes and the total reaction time was 10 minutes. During this period the temperature rose to a maximum of +0.8° C. with the cooling bath at −23° C. The reaction was discontinued when heat evolution had definitely ceased.

Isolation of the diazoacetic ester was accomplished by pouring the reaction mixture into a cold (0° C.) separatory funnel and rapidly separating the yellow-green methylene chloride solution into 1000 parts of cold 5% sodium bicarbonate solution. The aqueous layer was extracted once with 100 parts of methylene chloride. The combined methylene chloride solutions were transferred to a separatory funnel and agitated for 5 minutes with the sodium bicarbonate solution until both layers remained at >pH 7. The organic phase was then separated and transferred to a clean, dry separatory funnel and dried by shaking for 5 minutes with 15 parts of anhydrous calcium chloride. The ethyl diazoacetate solution was filtered through a cotton plug inserted in the separatory funnel stem. The solvent was removed from this filtered solution by distillation through an 18" packed column at a pressure of about 350 mm. The last traces of solvent were removed at a final pressure of 20 mm. and a maximum pot temperature of 35° C. The product consisted of 97.7 parts (85.8% of the theoretical yield) of a yellow oil with a refractive index of n_D^{25} 1.4611. A 25 part sample of this product on further distillation through an 8" column packed with Fenske rings yielded a middle cut of 11 parts, distilling at 32.2° C./7 mm. and possessing a refractive index of n_D^{25} 1.4616.

Example II

By the above procedure of Example I, ethyl diazoacetate was prepared in 93.5% yields by using in place of methylene chloride as a solvent 849 parts of ethylene dichloride—755 parts in the diazotization step and 94 parts in the extraction step. During the diazotization, the temperature of the reaction mixture was allowed to rise as high as 8.5° C.

Example III

Ethyl diazoacetate was prepared in 78.5% yield employing the procedure described under Example I, and using as a solvent a total of 1077 parts of carbon tetrachloride in place of methylene chloride (957 parts in the diazotization step and 120 parts in the extraction step). The maximum temperature of the reaction mixture during the diazotization was 3.5° C.

Example IV

In this preparation of ethyl diazoacetate the procedure of Example I was again followed using the total of 966 parts—859 parts in the diazotization step and 157 parts in the extraction step—of ethyl bromide in place of methylene chloride. The temperature of the reaction mixture during diazotization was allowed to rise to 2.5° C. A yield of 92.1 parts (80.7% of the theoretical yield) of ethyl diazoacetate was thus obtained.

Example V

Decyl diazoacetate was obtained in accordance with the procedure given under Example I by starting the decyl glycinate hydrochloride instead of the ethyl glycinate hydrochloride. The yield of crude amber-colored oil amounted to 81% of the theoretical amount. Molecular distillation of this crude product yielded a yellow oil boiling between 29.5° C./0.02 mm. and 40° C./0.04 mm. and possessing a refractive index of n_D^{25} 1.4610.

Anal, calc'd. for $C_{12}H_{22}N_2O_2$: N, 12.5. Found: N, 12.23, 12.02.

Example VI

Methyl diazoacetate was prepared by the general procedure described in Example I using as reactants 62.8 parts of methyl glycinate hydrochloride, 48.3 parts of sodium nitrite, 34 parts of sodium acetate trihydrate as a buffer, 401 parts of methylene chloride and 200 parts of water. The acid reactant consisted of 48 parts of sodium bisulfate monohydrate ($NaHSO_4.H_2O$) dissolved in 50 parts of water. After complete removal of the methylene chloride, 45.5 parts (91% of the theoretical yield) of methyl diazoacetate remained as a yellow oil. Extreme caution should be exercised in handling methyl diazoacetate since it has been found to detonate with great violence upon rapid heating.

By a procedure similar to that described in Example I in which the 5% sulfuric acid was replaced by an aqueous solution of sodium bisulfate monohydrate, ethyl diazoacetate was obtained in 88% yield.

Ethyl diazoacetate was also prepared in 67% yields by the procedure of Example I in which the dilute sulfuric acid was replaced by glacial acetic acid. The distilled ester boiled at 42–43° C./10–11 mm.

Example VII

In a glass reactor equipped with a rubber sealed stirrer and a short column for distillation, a mixture of 75.1 parts of glycine, 297 parts of n-butanol were saturated with hydrogen chloride while stirring and heating on a steam bath. Heating was continued for 40 minutes after the glycine had gone into solution (1.5 hours total time). The excess butanol was distilled off in vacuo on the steam bath and to remove the last traces, 87 parts of dry toluene was added and the operation continued until no more distillate came over.

To the cold butyl glycinate hydrochloride remaining as a viscous syrup in the flask, there was added 1000 parts of crushed ice, 802 parts of methylene chloride, and 83 parts of sodium nitrite while stirring. With the temperature at −10° C. and after flushing out the flask with nitrogen, 34.8 parts of sodium bisulfate monohydrate dissolved in 72 parts of water was added over a course of

15 minutes while stirring. During this time the temperature rose to 0.6° C. and the pH dropped to approximately 2. After stirring for 3 more minutes the mixture was transferred to a cold (0° C.) separatory funnel and the methylene chloride layer dropped into 1000 parts of 5% aqueous sodium bicarbonate solution. The water layer was extracted with 100 parts of methylene chloride and the combined methylene chloride solutions were well shaken with a sodium bicarbonate solution until the aqueous phase was yellow and both layers remained at above pH 7. After washing neutral with water (3 washes), the methylene chloride solution was dried over calcium chloride and the solvent distilled off through an 18" column under reduced pressure (10 to 25 mm.). The yield of butyl diazoacetate, a yellow oil, amounted to 117.5 parts (83% of the theoretical yield). This product had a refractive index of n_D^{25} 1.4592. Distillation of this product yielded a golden-yellow oil boiling at 42–43.2° C./3 mm. which possessed a refractive index of n_D^{25} 1.4597.

Example VIII

Hexyl glycinate hydrochloride was prepared from glycine and n-hexanol in the same manner as described in Example VII from 46.5 parts of glycine and 466 parts of hexanol. The diazotization was carried out by a procedure similar to that described under Example I but using 30.4 parts of 10% sulfuric acid instead of the 5% sulfuric acid of Example I. The yield of n-hexyl diazoacetate amounted to 96.3% of the theoretical of the reddish-brown oil with a refractive index of n_D^{25} 1.4577. Molecular distillation of this ester yielded a light yellow oil of refractive index n_D^{25} 1.4594.

Anal. cal'd. for $C_8H_{14}N_2O_2$: N, 16.5. Found: N, 16.22, 16.26.

2-ethylhexyl diazoacetate was obtained in 88.5% yield by the same procedure described for the n-hexyl analog starting with the 2-ethylhexyl glycinate hydrochloride. The product distilled as a yellow oil at 21–29° C./0.01 mm. and possessed a refractive index of n_D^{25} 1.4607.

Anal. cal'd. for $C_{10}H_{18}N_2O_2$: N, 14.13. Found: N, 13.94, 14.11.

Other aliphatic halogenated hydrocarbon solvents especially suitable for use in this invention, in addition to those in the examples, include methylene bromide, trichloroethylene, tetrachloroethylene, 2,2-difluoro-1-chloroethane, 2,2-difluoro-1,1-dichloroethane, methyl iodide, ethyl iodide and the like. The amount of solvent used should be sufficient to dissolve all the diazoacetic ester being formed and will depend on the temperature and the particular aliphatic halogenated hydrocarbon solvent which is used, as well as the specific diazoacetic ester being prepared. It is generally suitable to employ 3 to 20 parts of the aliphatic halogenated hydrocarbon solvent for each part of the glycine ester diazotized.

The nitrite used for diazotization, which is preferably sodium or potassium nitrite, should be present in an amount of at least one mole of nitrite for each mole of glycine ester salt. In general, it is preferred to use a 20–30% molar excess of sodium nitrite in an aqueous solution sufficient to substantially completely dissolve the nitrite at the temperature of diazotization. Aqueous solutions of 25–40% of the nitrite are preferably employed.

Among the mineral and organic acids and their acid salts which can be used as the acid reactants may be mentioned sulfuric acid, glacial acetic acid and sodium bisulfate monohydrate. The amount and concentration used are dependent on the particular acid reactant employed. Ordinarily from 0.04 mole to 0.6 mole of acid reactant per mole of glycine ester is suitable. With a strong mineral acid, such as sulfuric acid, only about 1/5 to 1/7 as much acid need be used as when employing sodium bisulfate monohydrate or glacial acetic acid. Although the organic acids, such as glacial acetic acid, are used at full strength, the strong mineral acids, such as sulfuric acid, are usually used in dilute aqueous solutions of preferably 5–20% concentration. However, the mineral acid salts, such as sodium bisulfate monohydrate, are most desirably employed in a 30–60% solution.

Buffers, such as sodium acetate, can be used in the process of this invention. However, the aliphatic halogenated hydrocarbon solvents used in this invention afford such complete protection to the diazoacetate from the acid solution that these buffers are not ordinarily necessary or, in many cases, even desirable.

The reaction time is relatively short and depends in part on the particular ester being diazotized, the solvent, and the size of the batch being treated. Substantially complete diazotization can be obtained in the presence of the aliphatic halogenated hydrocarbon solvents of this invention in a period varying from 5 minutes to not more than several hours. In general, the temperature of diazotization should be kept below 15° C., and preferably at −5° to 10° C.

The diazoacetic esters prepared by the process of this invention are very reactive and versatile intermediates, and are particularly useful in the synthesis of pharmaceuticals and insecticides.

As many apparently widely different embodiments of this invention may be made without departing from the spirit and scope thereof, it is to be understood that the invention is not limited to the specific embodiments thereof except as defined in the appended claims.

I claim:

1. In a process for diazotizing glycine esters, the steps of diazotizing in a solvent a glycine ester having the formula NH_2CH_2COOR wherein R is a hydrocarbon radical, said solvent being selected from a member of the group consisting of the ethylenically unsaturated and saturated liquid aliphatic halogenated hydrocarbons of from one to two carbon atoms, and recovering therefrom the resulting diazoacetic ester.

2. In a process for diazotizing glycine esters, the steps of diazotizing in a solvent a glycine ester having the formula NH_2CH_2COOR wherein R is a hydrocarbon radical, said solvent consisting of a liquid ethylenically unsaturated aliphatic halogenated hydrocarbon of from one to two carbon atoms, and recovering therefrom the resulting diazoacetic ester.

3. In a process for diazotizing glycine esters, the steps of diazotizing in a solvent a glycine ester having the formula NH_2CH_2COOR wherein R is a hydrocarbon radical, said solvent consisting of a liquid saturated aliphatic halogenated hydrocarbon of from one to two carbon atoms, and recovering therefrom the resulting diazoacetic ester.

4. In a process for diazotizing glycine esters, the steps of diazotizing in a solvent a glycine ester having the formula NH_2CH_2COOR wherein R is a saturated hydrocarbon radical, said solvent consisting of a liquid saturated aliphatic halo-

genated hydrocarbon of from one to two carbon atoms, and recovering therefrom the resulting diazoacetic ester.

5. In a process for diazotizing glycine esters, the steps of diazotizing in a solvent a glycine ester having the formula NH_2CH_2COOR wherein R is a saturated hydrocarbon radical, said solvent consisting of methylene chloride, and recovering therefrom the resulting diazoacetic ester.

6. In a process for diazotizing glycine esters, the steps of diazotizing in a solvent a glycine ester having the formula NH_2CH_2COOR wherein R is an alkyl radical, said solvent consisting of a liquid saturated halogenated hydrocarbon of from one to two carbon atoms, and recovering therefrom the resulting diazoacetic ester.

7. In a process for diazotizing glycine esters, the steps of diazotizing in a solvent a glycine ester having the formula NH_2CH_2COOR wherein R is an alkyl radical, said solvent consisting of methylene chloride, and recovering therefrom the resulting diazoacetic ester.

8. In a process for diazotizing glycine esters, the steps of diazotizing in a solvent a glycine ester having the formula NH_2CH_2COOR wherein R is an alkyl radical, said solvent consisting of carbon tetrachloride, and recovering therefrom the resulting diazoacetic ester.

9. In a process for diazotizing glycine esters, the steps of diazotizing in a solvent a glycine ester having the formula NH_2CH_2COOR wherein R is an alkyl radical, said solvent consisting of ethylene dichloride, and recovering therefrom the resulting diazoacetic ester.

10. In a process for diazotizing glycine esters, the steps of diazotizing in a solvent ethyl glycinate, said solvent consisting of methylene chloride, and recovering therefrom the resulting ethyl diazoacetate.

11. In a process for diazotizing glycine esters, the steps of diazotizing in a solvent ethyl glycinate, said solvent consisting of carbon tetrachloride, and recovering therefrom the resulting ethyl diazoacetate.

12. In a process for diazotizing glycine esters, the steps of diazotizing in a solvent ethyl glycinate, said solvent consisting of ethylene dichloride, and recovering therefrom the resulting ethyl diazoacetate.

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REFERENCES CITED

The following references are of record in the file of this patent:

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